Spotlight on mRNA – Regulation of mRNA vaccines and therapies

mRNA: a new era in genetic medicine?

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Regulation of mRNA vaccines and therapies

Earlier in this series we considered some of the potential uses of synthetic mRNA to prevent or treat diseases. In this article, we take another look at these uses and set out how mRNA therapies are currently regulated, with a focus on the much publicised mRNA COVID-19 vaccinations. Finally, we consider the potential for regulatory flexibility in this exciting and rapidly developing area.

As set out in previous articles, mRNA technology can essentially be viewed as a consisting of two parts: (1) the delivery system and (2) the coded mRNA itself. The delivery system ensures the mRNA gets into the intended cells in the body effectively and safely. The mRNA component corresponds to the specific genetic sequence of the protein or antigen you want the cells to produce. This two component model is central to the current debate around the approval and regulation of mRNA therapies and how to apply the existing framework to these therapies.

Medicine authorisation routes

The regulatory starting point in the EU and UK for mRNA therapies is that they are regulated as human medicines. There are some specific considerations for each type of therapy but in general they are regulated by the same legislation that applies to most medicines, from over-the-counter household names such as paracetamol to ground breaking gene therapies such as Zolgensma.

There is specific additional legislation for therapies classed as advanced therapy medicinal products (ATMPs)[1]. ATMPs include gene therapy medicinal products, somatic cell therapy medicinal products and tissue engineered products. At present, the only mRNA therapies to have received regulatory approval are the vaccines against COVID-19. Vaccines are specifically excluded from the definition of a gene therapy medicinal product and therefore these mRNA therapies are not classed as ATMPs. Future mRNA therapies may well be regulated by the ATMP legislation and therefore subject to the additional requirements this entails but this will depend on the scientific intricacies underpinning each therapy.

All medicines must be authorised by the relevant regulator, the MHRA in the UK and the European Medicines Agency (EMA) in the EU, before they can be put on the market. Usually this authorisation takes the form of a marketing authorisation (MA).

In the EU there are two main routes for authorising medicines, the centralised route and the national route. Prior to Brexit, medicines approved through a European route could be placed on the British market. However, from 1 January 2021, changes to the UK procedures took effect and now there are several different pathways to securing a MA in the UK.

Applications for MAs for medicines containing new active substances must be accompanied by supporting data, including the results of pharmaceutical tests, preclinical tests and clinical trials, as well as relevant published literature. The application requirements for medicines containing existing active substances is less onerous and applicants can rely on data of an appropriate reference medicine.

The regulator considers all the information included in the application and then makes the decision to grant or refuse the MA. If granted, the authorisation will come with a number of different continuing obligations such pharmacovigilance reporting.

COVID-19 mRNA vaccine approval

There are some other, significantly lesser used, pathways to market for medicines that exist outside of the conventional procedures described above. These routes received significant publicity in the battle against the COVID-19 pandemic as they were used to expedite the approval of the mRNA vaccines developed by Pfizer/BioNTech and Moderna in the UK and the EU.

In the EU, both mRNA vaccines were granted conditional marketing authorisations (cMAs). Despite its name, a cMA is not an MA subject to conditions. The cMA is reserved for unusual medicines or scenarios and can only be used for an unmet medicinal need. A cMA is granted for a period of 12 months and can be renewed following a review by the EMA of supplementary information. The cMA holder is obliged to collect and present updated, follow-up data, and the cMA can be converted into a full MA. At present neither of the cMAs granted for either mRNA vaccine have been converted to

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MA. However, the initial 12 months granted have not yet expired.

In the UK, both mRNA vaccines were granted temporary regulatory authorisation under Regulation 174 of the Human Medicine Regulations 2012. This route allows the MHRA to authorise, on a temporary basis, the supply of a medicinal product in response to the spread of pathogenic agents which may cause harm to human beings[2]. Unlike the cMA route in the EU there are no formal criteria to be satisfied before a grant of an authorisation under Regulation 174 and there is no formal time limit on such authorisation. We note that both Regulation 174 approvals were subject to specific conditions which included the manufacturers being required to provide the MHRA with further generated data. We note that cMAs are available in the UK and are assessed by the MHRA in the same way as they are in Europe but they were not introduced until 1 January 2021. At the time the MHRA approved the vaccines under Regulation 174, cMAs could only be granted by the EMA.

"Plug and play" technology – flexible regulation

The two component system described at the beginning of this article is present in all types of mRNA therapy and has been described by commentators as "plug and play" technology. The different potential therapies involving mRNA listed in previous articles primarily differ not due to the technique involved but in the outcome that is achieved. For example a mRNA gene therapy, which triggers the expression of proteins naturally missing as a result of genetic defects, and an mRNA vaccine, which produces a specific antigen which in turn is recognised by the immune system, are both comprised of a delivery system and specifically coded mRNA.

The nature of this technology has given rise to several questions regarding how the medicines regulatory framework applies, for example, most urgently, in the context of COVID-19. Soon after the introduction of the first vaccines, evidence that new mutations or variants of the SARS-CoV-2 coronavirus could evade the protection resulting from the vaccines or previous infections emerged. The scientific community immediately began work on potential updates to the vaccines to counter these new and more infectious strains, but the question of how these updated vaccines could be introduced and importantly authorised arose.

The new variants differ from the original, "wild type" coronavirus in that the mutation in the virus primarily causes changes to the virus' spike protein, the part which helps it enter human cells. The genetic code for each of these variants is slightly different and results in their different risk profiles. The vaccines were designed to trigger the production of specific antigens which in turn would then instruct cells to produce the virus' spike protein. Initially, the mRNA sequence contained in the vaccine corresponded to the "wild type" spike protein, but this could be easily updated to match that of reported or even predicted, future variants.

Regulators could consider a change in the mRNA code of an authorised vaccine as a new medicinal product, requiring new clinical trials to demonstrate safety, efficacy and immunogenicity to be conducted. This interpretation would result in significant delays in getting the updated vaccine deployed to patients, potentially even resulting in the updated vaccine being outdated by the time it was approved as the virus could mutate further. In the context of COVID-19 vaccines, regulators have chosen a less conservative interpretation, balancing the requirement for evidence of quality, efficacy and safety with the need for speed in the fight against a highly infectious pathogen.

However, this is not an unprecedented situation for the regulators, who acknowledged as much earlier this year. At the end of February 2021, the EMA issued guidance on the regulatory requirements for vaccines intended to provide protection against variant strain(s) of SARS-CoV-2[3]. The MHRA, hot on the EMA's heels, published a guidance paper at the start of March on strain changes in authorised COVID-19 vaccines[4]. The EMA followed up the guidance published a month later with a press release, explanatory memorandum and a delegated EU regulation on a new procedure to facilitate and speed up approval of adapted COVID-19 vaccines[5]. Both the EMA's and the MHRA's releases cited the regulatory approach to adaptations of human influenza vaccines as key to striking the right balance.

Influenza viruses are subject to constant mutational changes. However the corresponding new flu vaccines are not required to undergo fresh trials. This is possible due to well established global infrastructure. A global network of labs share information on influenza viruses circulating in the population, including genomic sequences, antigenic features and epidemiological data. The WHO then use this data to make biannual recommendations on vaccine composition. This allows industry to get a head start on potentially prevalent strains. Pharmaceutical quality, safety, immunogenicity and efficacy data can be generated on these pre-pandemic strains and the vaccine can be tweaked at the time a dangerous strain is identified, without requiring the same amount of data to be submitted to the regulator.

The approach to influenza vaccines has developed over decades of experience in tackling seasonal virus variants, something which is simply not present in the fight against COVID-19. Some trials and data will be required but the size and duration of these studies will depend on whether sufficient correlations with the original, trialled vaccine data can be identified.

In the EU, the delegated regulation passed in March 2021[6] amended the regulation on the examination of variants to the terms of marketing authorisations for medicines[7] and states that "the Commission may, where certain pharmaceutical, non-clinical or clinical data are missing, exceptionally and temporarily accept a variation to the terms of a marketing authorisation for a human influenza vaccine or a human coronavirus vaccine."

Conclusions

The UK and EU regulators' responses to COVID-19 does demonstrate some willingness to apply the medicines regulatory framework with a degree of

flexibility. However, this must be read in the highly unusual circumstances of a global pandemic.

Earlier in this series, we described some of the other potential therapies, outside of vaccines, incorporating mRNA technology. As above, whether these future, non-vaccine, mRNA therapies are regulated under human medicines legislation or as ATMPs will depend on the specifics of each therapy.

Missed out? Read the other articles in this Spotlight on mRNA series:

- A brief history of mRNA research
- What is mRNA and what can it be used for?
- IP landscape
- Recent deal activity

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[1] Regulation (EC) No 1394/2007
[2] The Regulation 174 route also allows temporary authorisation in response to toxins, chemical agents or nuclear radiation.
[3] https://www.ema.europa.eu/en/regulatory-requirements-vaccines-intended-provide-protection-against-variant-strains-sars-cov-2
[4] https://www.gov.uk/government/publications/access-consortium-guidance-on-strain-changes-in-authorised-covid-19-vaccines/guidance-on-strain-changes-in-authorised-covid-19-vaccines
[5] https://ec.europa.eu/commission/presscorner/detail/en/ip_21_1088
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